APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,743	12/12/2000	Wei-min Liu	3298.1	7518

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EXAMINER
ALLEN, MARIANNE P

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

<table>
<tr><td colspan="2" rowspan="2">Office Action Summary</td><td>Application No.</td><td colspan="2">Applicant(s)</td></tr>
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<tr><td colspan="2"></td><td>Marianne P. Allen</td><td>1631</td><td></td></tr>
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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-102* is/are pending in the application.

    4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

    If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All b)☐ Some * c)☐ None of:

        1.☐ Certified copies of the priority documents have been received.

        2.☐ Certified copies of the priority documents have been received in Application No. _____ .

        3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

    a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *4* .

4)☐ Interview Summary (PTO-413) Paper No(s). _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

Claims 1-102 are rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention.

Claim 1 requires a test statistic. Page 29 provides three statistics that can be used to make

calls based on one sided Wilcoxon's signed rank tests as set forth in claim 1. The third test does

not use mismatch intensity values and thus could not be used for this method. The second test is

also known as Ryder's discrimination score. The specification does not provide guidance on

selecting other test statistics for use in the claimed method nor the associated threshold values. It

would require undue experimentation for one of ordinary skill in the art to derive additional test

statistics that would be appropriate for use in the claimed method. Likewise with respect to

claim 26, the only test statistic disclosed using perfect match intensity values and background

intensity values is given on page 29, the third test. The specification does not provide guidance

on selecting other test statistics with these variables and again would require undue

experimentation for one of ordinary skill in the art to derive additional test statistics. It is noted

with respect to Ryder's discrimination score on page 29 that H_1 appears to in error as the median

$(PM_i-MM_i/(PM_i-MM_i)$ would always be 1. Note that this is inconsistent with Figure 6 although

Figure 6 also appears to contain an error in that there are two H_0 and no H_1. Applicant is

cautioned against introducing new matter.

Claim 1 requires a threshold value without reciting how it is determined. Claims 4 and 5 recite two different equations for calculating the threshold value. It appears that τ_1 is the threshold value but the claims do not make this clear. Nevertheless, the specification does not disclose the value of the constant, c_1, nor does it provide guidance on how to determine or calculate the constant. Page 24 gives another equation for threshold; however, several of the variables are undefined. The examples provide particular threshold values for the particular experiments performed but does not disclose how they were selected or computed. In particular, page 40 discloses the parameter with respect to Equation (3c) where $c''_1 = 1.2$. Note that this equation and constant notation do not appear to be present in the specification. Likewise, claim 26 requires a threshold. Claims 27, 29, and 30 disclose equations for calculating the threshold for the aforementioned testing statistic; however, the specification does not disclose the value of the constant, nor does it provide guidance on how to determine or calculate the constant. With the exception of where the threshold is zero or specifically provided, one of ordinary skill in the art would not know what threshold to use or how to determine it.

Claims 1 and 26 require indicating whether said transcript is present based upon said p-value. The claim does not recite those p-values that would indicate presence or absence. The specification on pages 5 and 29 states that the presence, marginal presence, and absence of a transcript is called based upon the p-value and significance values. The significance values, particularly as discussed in page 5, are not limitations of the claims. Although the specification provides particular significance values, it does not provide guidance on selecting or choosing others that would result in a correct determination of the presence or absence of the transcript. Note that the significance values provided appear to be derived from the examples which used

Ryder's discrimination score as the test statistic. How these values were selected or chosen is not disclosed. Note that the examples make clear that false positives and false negatives can occur. The claims are considered to be directed to determining the correct answer with respect to presence or absence and eliminating false positives and false negatives. As such, the parameters that would provide such a result must be taught and the claims must contain limitations that would lead to this result.

As written, claims 1 and 26 and many of the dependent claims lack critical features including the requirement for significance levels as well as the conclusions to be drawn (present, absent) from any particular p-value.

While the above comments are directed to the methods represented by claims 1 and 26 and their dependent claims, the comments are equally applicable to the corresponding computer software products of claims 39 and 64 and their dependent claims as well as the corresponding systems of claims 77 and 102 and their dependent claims.

Claims 10, 12, 14-25, 29, 35-63, and 77-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is confusing as written as the first and second significance levels overlap. (See claims 7-8 upon which claim 10 depends.) See also claims 22, 35, 48, 60, 73, 86, and 98.

Claim 12 lacks antecedent basis in claim 1 for significance levels. In addition, claim 1 is directed to determining presence and not indicating marginal detection. See also claims 24, 37, 50, 62, 75, 88, and 100.

Claim 14 recites a testing statistic $median((PM_i-MM_i/(PM_+MM_i))$. This appears to be an erroneous formula. It is inconsistent with similar formulas on pages 5, 7, 10, and Figure 6. Note that the notation is inconsistent among all of these formulas. Applicant is cautioned against introducing new matter. See also claim 90.

Claim 29 recites the subscript "1." This is inconsistent with the specification which recites the subscript "3" in this context. See page 31. Clarification is requested. See also claim 67.

Claim 39 is confusing in reciting "a computer readable media for storing said computer program codes." This language does not make clear if the computer readable media is actually storing the code. Claim 39 is further confusing in reciting three different computer program codes. It is unclear whether the software product of the preamble is an integrated product where the results of one program code are used as input for the next computer program code or whether these are three discrete pieces of software. See also claim 64.

Claim 43 is confusing in its dependency on claim 42. This appears to be an error in that it would require computation of two different thresholds simultaneously.

Claim 52 recites a testing statistic $median((PM_i-MM_i/(PM_i-MM_i))$. Although this is consistent with the formula on page 33, it appears to be erroneous. Note that as written, the value would always be 1. It is inconsistent with Figure 6. Applicant is cautioned against introducing new matter.

Claim 77 is confusing in reciting "said logical step comprising." This is inconsistent

with the plurality of logical steps required. See also claim 102.

Claims 90 and 91 are confusing in their dependency upon claims 76-77, respectively.

Claims 76 and 77 are not directed to systems. They are directed to software products.

Claim 102 is confusing in reciting "A processor" and "A memory" in the middle of the

claim. It appears that "A" should be lowercase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in
> section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are
> such that the subject matter as a whole would have been obvious at the time the invention was made to a person
> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the
> manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the

claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c)

and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 39, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Lockhart et al. (1996) in view of either Hogg et al. or Hollander et al.

Lockhart et al. disclose quantitative analysis of the signal intensity of PM and MM pairs from an array hybridization experiment. The results are used to make a determination of the presence or absence of a nucleic acid. The average of the logarithm of the PM/MM ratios for each probe set is computed along with the number of instances in which the PM hybridization signal is larger than the MM signal. The decision matrix used is not disclosed. The quantitative analysis is performed on a computer system using appropriate software. (See page 1679.) The reference does not disclose calculating a p-value using a Wilcoxon's signed rank test.

Hogg et al. and Hollander et al. discloses the Wilcoxon's signed rank test and its use for non-parametric data.

One of ordinary skill in the art would have been aware that hybridization data from nucleic acid arrays was nonparametric data. As such, it would have been obvious to use known nonparametric statistical analysis to analyze the results of multiple probe experiments for perfect match and mismatch probes. Lockhart et al. discloses a method for determining the presence or absence of a nucleic acid using signal information from PM and MM hybridization signals. It would have been obvious to use the difference between the PM and MM signals for each probe set as the test statistic in the Wilcoxon's signed rank test to determine presence or absence of the nucleic acid. Such statistical analysis would have been routinely performed using computer systems and appropriate software.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 703-308-0666. The examiner can normally be reached on Monday-Friday, 8:30 am - 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone numbers for

the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa
November 4, 2002